CLAIMS

We claim:

1. A method of generating an animal model exhibiting a pathological condition of Alzheimer's disease, comprising:
   (a) inducing a transient forebrain ischemia in the animal; and
   (b) allowing the animal to recover from the ischemic induction for a sufficient amount of time so that a pathological condition of Alzheimer's disease is exhibited.

2. The method of claim 1, wherein the animal is selected from the group consisting of mammal, primate, and rodent.

3. The method of claim 1, wherein the animal is rat.

4. The method of claim 1, wherein the animal is selected from the group consisting of mouse, guinea pig, dog, cat, rabbit, pig, chimpanzee, and monkey.

5. The method of claim 1, wherein the pathological condition is characterized by differential expression of an Alzheimer's disease-associated gene or polypeptide.

6. The method of claim 5, wherein the Alzheimer's disease-associated polypeptide is a beta-amyloid peptide.

7. The method of claim 5, wherein the Alzheimer's disease-associated gene or polypeptide is beta-secretase.

8. The method of claim 5, wherein the differential expression of an Alzheimer's disease-associated polypeptide is detected by an immunoassay.

9. The method of claim 5, wherein the differential expression of an Alzheimer's disease-associated polypeptide is detected by a hybridization assay.

10. The method of claim 1, wherein the animal is allowed to recover for at least about 2 weeks.

11. The method of claim 1, wherein the animal is allowed to recover for at least about 4 weeks.

12. The method of claim 1, wherein the animal is allowed to recover for about 2 to about 10 weeks.

13. The method of claim 1, wherein the animal is allowed to recover for about 4 to about 10 weeks.

14. The method of claim 1, wherein the ischemic induction lasts for more than 10 minutes.

15. The method of claim 1, wherein the ischemic induction lasts for about 15 minutes to about 20 minutes.

16. An animal model generated by the method of claim 1.

17. A method of developing a modulator of pathogenesis of Alzheimer's disease, comprising:

(a) administering a candidate modulator to a test animal model generated by a method comprising (i) inducing a transient and reversible forebrain ischemia in the animal; and (ii) allowing the animal to recover from the ischemic induction for a sufficient amount of time so that a pathological condition of Alzheimer's disease is exhibited; and

(b) detecting a change in the pathological condition in the test animal model of (a) relative to a control.

18. The method of claim 17, wherein the modulator ameliorates the pathological condition of Alzheimer's disease.

19. The method of claim 17, wherein the modulator advances the pathological condition of Alzheimer's disease.

20. The method of claim 17, where the pathological condition is characterized by differential expression of an Alzheimer's disease-associated gene or polypeptide.

21. The method of claim 20, where the Alzheimer's disease-associated polypeptide is a beta-amyloid peptide.

22. The method of claim 20, where the Alzheimer's disease-associated gene or polypeptide is beta-secretase.

23. The method of claim 20, wherein the differential expression of an Alzheimer's disease-associated polypeptide is detected by an immunoassay.

24. The method of claim 20, wherein the differential expression of an Alzheimer's disease-associated gene is detected by a hybridization assay.

25. The method of claim 17, where the pathological condition is selected from the group consisting of beta-amyloid plaque formation, plaque-induced mononuclear phagocyte activation, plaque-induced mononuclear phagocyte neurotoxicity, and neuronal loss within the brain.

26. The method of claim 17, wherein the candidate modulator is selected from the group consisting of an antisense oligonucleotide, a ribozyme, a ribozyme derivative, an antibody, a liposome, a small interfering RNA, a small molecule and an inorganic compound.

27. The method of claim 17, wherein the test animal model is selected from the group consisting of mammal, primate, and rodent.

28. The method of claim 17, wherein the animal is selected from the group consisting of rat, mouse, guinea pig, dog, cat, rabbit, pig, chimpanzee, and monkey.

29. The method of claim 17, wherein the control is an animal to which the candidate modulator is not administered or is administered at a lower dose, or is administered for a shorter period of time, relative to the test animal model.

30. The method of claim 17, wherein the control also exhibits the pathological condition of Alzheimer's disease.

31. The method of claim 30, wherein the control is generated by (i) inducing a transient forebrain ischemia in the animal; and (ii) allowing the animal to recover from the ischemic induction for a sufficient amount of time so that a pathological condition of Alzheimer's disease is exhibited

32. The method of claim 17 or 31, wherein the ischemic induction lasts more than 10 minutes.

33. The method of claim 17 or 31, wherein the ischemic induction lasts about 15 to about 20 minutes.

34. The method of claim 17, wherein the animal is allowed to recover for at least about 2 weeks.

35. The method of claim 17, wherein the animal is allowed to recover for at least about 4 weeks.

36. The method of claim 17, wherein the animal is allowed to recover for about 2 to about 10 weeks.

37. The method of claim 17, wherein the animal is allowed to recover for about 4 to about 10 weeks.

38. The method of claim 17, where the candidate modulator is administered to the test animal model intravenously.

39. The method of claim 17, where the candidate modulator is administered to the test animal model subcutaneously, intramuscularly, intraperitoneally, intradermally, orally, intranasally, or intrapulmonarily.

40. A method of developing a modulator of an Alzheimer's disease-associated gene or protein, comprising:

(a) contacting a candidate modulator with an Alzheimer's disease-associated gene or protein that is contained in a test biological sample derived from an animal model, wherein the animal model is generated by a method comprising:

(i) inducing a transient forebrain ischemia in the animal; and

(ii) allowing the animal to recover from the ischemic induction for a sufficient amount of time so that a pathological condition of Alzheimer's disease is exhibited; and

(b) detecting an alteration in expression of the Alzheimer's disease-associated gene or protein, or an alteration in activity of the protein of step (a), relative to a control sample.

41. The method of claim 40, wherein the modulator ameliorates the pathological condition of Alzheimer's disease.

42. The method of claim 40, wherein the modulator advances the pathological condition of Alzheimer's disease.

43. The method of claim 40, where the pathological condition is characterized by differential expression of an Alzheimer's disease-associated gene or polypeptide.

44. The method of claim 40, where the Alzheimer's disease-associated polypeptide is a beta-amyloid peptide.

45. The method of claim 40, where the Alzheimer's disease-associated gene or polypeptide is beta-secretase.

46. The method of claim 40, where the pathological condition is selected from the group consisting of beta-amyloid plaque formation, plaque-induced mononuclear phagocyte activation, plaque-induced mononuclear phagocyte neurotoxicity, and neuronal loss within the brain.

47. The method of claim 40, wherein the alteration in expression of the Alzheimer's disease-associated gene is assayed by a hybridization assay.

48. The method of claim 40, wherein the alteration in expression of the Alzheimer's disease-associated protein is detected by an immunoassay.

49. The method of claim 40, wherein the candidate modulator is selected from the group consisting of an antisense oligonucleotide, a ribozyme, a ribozyme derivative, an antibody, a liposome, a small interfering RNA, a small molecule and an inorganic compound.

50. The method of claim 40, wherein the test animal model is selected from the group consisting of mammal, primate, and rodent.

51. The method of claim 40, wherein the animal is selected from the group consisting of rat, mouse, guinea pig, dog, cat, rabbit, pig, chimpanzee, and monkey.

52. The method of claim 40, wherein the ischemic induction lasts more than 10 minutes.

53. The method of claim 40, wherein the ischemic induction lasts about 15 to about 20 minutes.

54. The method of claim 1, wherein the animal is an aged animal.